FORM PCT 1390
REV. 5/93

U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

ATTORNEY'S DOCKET NO
JOMAA-4 (PCT)

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

U.S. APPLICATION NO. (if known, see 37 CFR 1.5)
09/868961

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/EP99/10350	23 DECEMBER 1999	23 DECEMBER 1998

TITLE OF INVENTION
USE OF BISPHOSPHONATES FOR THE PREVENTION AND TREATMENT OF INFECTIOUS PROCESSES

APPLICANT(S) FOR DO/EO/US
HASSAN JOMAA

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. X This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ___ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. X This is an express request to begin national examination procedures (35 U.S.C. 371 (f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).
4. X A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. X A copy of the International Application as filed (35 U.S.C. 371(c)(2)
   a. ___ is transmitted herewith (required only if not transmitted by the International Bureau)
   b. X has been transmitted by the International Bureau.
   c. ___ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. X A translation of the International Application into English (35 U.S.C. 371(c)(2)).
7. ___ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3)).
   a. ___ are transmitted herewith (required only if not transmitted by the International Bureau).
   b. ___ have been transmitted by the International Bureau.
   c. ___ have not been made; however, the time limit for making such amendments has **NOT** expired.
   d. ___ have not been made and will not be made.
8. ___ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. X An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. ___ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. to 16. below concern other document(s) or information included:

11. ___ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. X An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. X A **FIRST** preliminary amendment.
    ___ A **SECOND** or **SUBSEQUENT** preliminary amendment.
14. ___ A substitute specification.
15. ___ A change of power of attorney and/or address letter.
16. X Other items or information:

    PCT/ISA/210 - Int'l. Search Report (English)

Applicant Claims Priority under 35 U.S.C. §119 of German Application No. 198 59 668.5 filed December 23, 1998.
Applicant Claims Priority under 35 U.S.C. §120 of: PCT/EP99/10350 filed December 23, 1999.

APPLICATION NO. (if known, see 37 CFR 1.5) 09/868961	INTERNATIONAL APPLICATION NO PCT/EP99/10350	ATTORNEY'S DOCKET NO JOMAA - 4 (PCT)

X The following fees are submitted:	CALCULATIONS	PTO USE ONLY
Basic National Fee (37 CFR 1.492(a)(1)-(5)):		
Search Report has been prepared by the EPO or JPO.....**$860.00**		
International preliminary examination fee paid to USPTO (37 CFR 1.482) **$690.00**		
Neither international preliminary examination fee paid (37 CFR 1.82) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO.....**$1,000.00**		
International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(2)-(4).....**$100.00**		
ENTER APPROPRIATE BASIC FEE AMOUNT =	$ 860.00	
Surcharge of **$130.00** for furnishing the oath or declaration later than ___ 20 ___ 30 months from the earliest claimed priority date (37 CFR 1.492(e)).		

Claims	Number Filed	Number Extra	Rate		
Total Claims	10 - 20 =	- 0 -	X **$18.00**	$	
Independent Claims	1 - 3 =	- 0 -	X **$80.00**	$	
Multiple dependent claim(s) (if applicable)			+ **$270.00**	$	
TOTAL OF ABOVE CALCULATIONS =				$ 860.00	
Reduction by 1/2 for Small Entity status.				$ 430.00	
SUBTOTAL =				$ 430.00	
Processing fee of **$130.00** for furnishing the English translation later than ___ 20 ___ 30 months from the earliest claimed priority date (37 CFR 1.492(f)). +				$	
TOTAL NATIONAL FEE =				$ 430.00	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). **$40.00** per property +				See cover sheet attached to assign $ to be charged to Deposit Acct	
TOTAL FEES ENCLOSED =				$ 430.00	
				Amount to be: refunded	$
				charged	$

X Applicant claims Small Entity status.

a. X A check in the amount of $ 430.00 to cover the above fees is enclosed.

b. ___ Please charge my Deposit Account No. 03-2468 in the amount of $_____ to cover the above fees. A duplicate copy of this sheet is enclosed.

c. X The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment, to Deposit Account No. 03-2468. A duplicate copy of this sheet is enclosed.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:
COLLARD & ROE, P.C.
1077 Northern Boulevard
Roslyn, New York 11576-1696
(516) 365-9802

Edward R. Freedman
Signature

Edward R. Freedman
Reg. No. 26,048

Express Mail No. **EL 769 393 133 US**
Date of Deposit June 22, 2001

I hereby certify that this paper or fee is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10, on the date indicated above, and is addressed to the Ass't. Commissioner for Patents, Washington, D.C. 20231

Lisa L. Vulpis
Lisa L. Vulpis

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANTS: HASSAN JOMAA - 4 (PCT)

PCT NO.: PCT/EP99/10350

FILED: DECEMBER 23, 1999

TITLE: USE OF BISPHOSPHONATES FOR THE PREVENTION AND TREATMENT OF INFECTIOUS PROCESSES

PRELIMINARY AMENDMENT

BOX PCT
Ass't. Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

Preliminary to the initial Office Action, please amend the above-identified application as follows:

IN THE ABSTRACT:

Please add the attached Abstract of the Disclosure on a separate page.

IN THE SPECIFICATION:

On Page 1, above line 1, please insert the following paragraphs:

--CROSS REFERENCE TO RELATED APPLICATIONS

Applicant claims priority under 35 U.S.C. §119 of German Application No. 198 59 668.5 filed December 23, 1998. Applicant also claims priority under 35 U.S.C. §120 of PCT/EP99/10350 filed

December 23, 1999. The international application under PCT article 21(2) was not published in English.--

Page 1, after formula (I), replace lines 7-26 with the following paragraphs:

--in which

A_1, A_2, A_3, A_4, which may be identical or different, are selected from the group which consists of hydrogen, metals of main groups I, II and III of the periodic system, such as Na, K, Ca, Mg, Al as well as substituted and unsubstituted ammonium and ammonium compounds derived from ethylenediamine or amino acids,
X is absent or is selected from the group which consists of alkylene with up to 9 carbon atoms, alkenylene with up to 9 carbon atoms, hydroxyalkylene with up to 9 carbon atoms and amidino,
R_1 is selected from the group which consists of H, OH, NH_2, $-CH_3$,
R_2 is selected from the group which consists of H, OH, $-NH_2$, substituted and unsubstituted acyl, substituted and unsubstituted alkyl, substituted and unsubstituted aryl, substituted and unsubstituted cycloalkyl, substituted and unsubstituted aralkyl, substituted and unsubstituted heterocyclic residue and the pharmaceutically compatible salts, amides, esters and salts of the esters or compounds which, on administration, form the

compounds to be administered as metabolites or breakdown products,--

Page 3, replace lines 8-14 with the following paragraphs:

--Preferably suitable substances of the formula (I) are those in which

A_1, A_2, A_3, A_4, which may be identical or different, are selected from the group which consists of hydrogen, metals of main groups I, II and III of the periodic system, such as Na, K, Ca, Mg, Al, substituted and unsubstituted ammonium and ammonium compounds derived from ethylenediamine or amino acids,

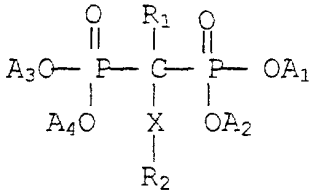
X is absent or is selected from the group which consists of alkyl, $(CH_2)_{1-6}$, in particular $(CH_2)_{1-5}$, and amidino,--

A marked-up version of the prior pending paragraphs showing the changes made is attached as Exhibit A.

IN THE CLAIMS:

Please cancel claims 1-11 and replace them with new claims 12-21 as follows:

--12. Use of bisphosphonic acids of the general formula



(I),

in which

A_1, A_2, A_3, A_4, which may be identical or different, are selected from the group which consists of hydrogen, metals of main groups I, II and III of the periodic system, such as Na, K, Ca, Mg, Al as well as substituted and unsubstituted ammonium and ammonium compounds derived from ethylenediamine or amino acids,

X is absent or is selected from the group which consists of alkylene with up to 9 carbon atoms, alkenylene with up to 9 carbon atoms, hydroxyalkylene with up to 9 carbon atoms and amidino,

R_1 is selected from the group which consists of H, OH, NH_2, $-CH_3$,

R_2 is selected from the group which consists of H, OH, $-NH_2$, substituted and unsubstituted acyl, substituted and unsubstituted alkyl, substituted and unsubstituted aryl, substituted and unsubstituted cycloalkyl, substituted and unsubstituted aralkyl, substituted and unsubstituted heterocyclic residue and

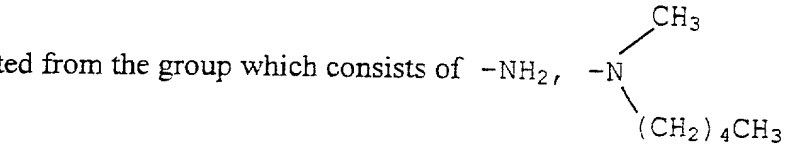
the pharmaceutically compatible salts, amides, esters and salts of the esters or compounds which, on administration, form the compounds to be administered as metabolites or breakdown products, for the production of pharmaceutical preparations for the inactivation of γδ-T cells for the prevention and treatment of diseases caused by parasites, viruses, bacteria and fungi with the exception of AIDS and AIDS-initiated inflammatory conditions and the sequelae thereof, namely degeneration of connective tissue.

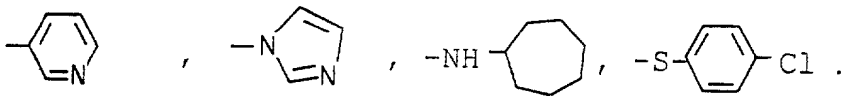
13. **Use according to claim 12, characterised in that**

A_1, A_2, A_3, A_4, which may be identical or different, are selected from the group which consists of hydrogen, metals of main groups I, II and III of the periodic system, such as Na, K, Ca, Mg, Al, substituted and unsubstituted ammonium and ammonium compounds derived from ethylenediamine or amino acids,

X is absent or is selected from the group which consists of alkyl, $(CH_2)_{1-6}$, in particular $(CH_2)_{1-5}$, and amidino,

R_1 is selected from the group which consists of H, OH, NH_2, $-CH_3$, and

R_2 is selected from the group which consists of $-NH_2$, 



14. Use according to claim 13,
characterised in that
the bisphosphonates are selected from the group which consists of amino-hydroxy-methylidene-bisphosphonic acid,
2-amino-1-hydroxyethylidene-1,1-bisphosphonic acid
3-amino-1-hydroxypropylidene-1,1-bisphosphonic acid,
4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid,
6-amino-1-hydroxyhexylidene-1,1-bisphosphonic acid,
amidinomethylene-bisphosphonic acid,
3-methylpentylamino-1-hydroxypropylidene-1,1-bisphosphonic acid,
2-(3-pyridinyl)-1-hydroxyethylidene-bisphosphonic acid,
1-hydroxy-2-(imidazol-1-yl)-ethylidene-1,1-bisphosphonic acid,
cycloheptylaminomethylenediphosphonic acid,
4-chlorophenyl-thiomethylene-1,1-bisphosphonic acid and the derivatives thereof.

15. Use according to claim 12 for the treatment and prophylaxis of acne vulgaris, tuberculosis in humans and animals, leprosy and further mycobacterioses in humans and animals, paratuberculosis in animals, Campylobacter enteritis infections in humans and animals, of Helicobacter pylori and Chlamydia for the prevention or treatment of cardiac and vascular diseases, in particular coronary cardiac disease.

16. Use according to claim 12 in the eradication of bacteria and viruses.

17. Use according to claim 16 for the eradication of Helicobacter pylori and Chlamydia.

18. Use according to claim 16 for the eradication of eradication of papillomaviruses to prevent tumours, in particular tumours of the reproductive organs caused by papillomaviruses in humans, eradication of herpesviruses, eradication of human herpesvirus 8 to treat Kaposi's sarcoma, eradication of cytomegaloviruses before transplantations, eradication of Epstein-Barr viruses before transplantation and to prevent tumours associated with Epstein-Barr viruses, eradication of hepatitis viruses to treat chronic liver disease and to prevent liver tumours and cirrhosis of the liver, eradication of coxsackie-viruses in cardiomyopathy, eradication of coxsackie-viruses in diabetes mellitus patients, eradication of immunodeficiency viruses in humans and animals, treatment of accompanying infections in AIDS patients, treatment of respiratory tract inflammation of viral causation (laryngeal papilloma, hyperplasia, rhinitis, pharyngitis, bronchitis, pneumonia), of the liver and gall system (hepatitis, cholangitis, hepatocellular carcinoma), of the lymphatic tissue (mononucleosis, lymphadenitis), of the haemopoietic system, of the skin (warts, dermatitis, herpes labialis, herpes febrilis, herpes zoster, shingles), of the mucous membranes (papillomas, conjunctival papillomas, hyperplasia, dysplasia), of the cardiovascular system (arteriitis, myocarditis, endocarditis, pericarditis), of the kidney/urinary system, of the reproductive organs (anogenital lesions, warts, genital warts, sharp condylomas, dysplasia, papillomas, cervical dysplasia, condyloma acuminatum, epidermodysplasia verruciformis), of the locomotory organs (myositis, myalgia), with the exception of AIDS and AIDS-initiated inflammatory conditions and the sequelae thereof, namely degeneration of connective tissue.

19. Use according to claim 18 for the eradication of the hepatitis C virus.

20. Use according to claim 12 in a pharmaceutical preparation which additionally contains a pharmaceutically acceptable excipient.

21. Use according to claim 12 as an adjuvant to vaccines. — —

REMARKS

By this Preliminary Amendment, the application has been amended to conform with U.S. practice, the cross-reference to related applications has been inserted on page 1, claims 1-11 have been canceled and replaced with new claims 12-21 and an Abstract has been provided. No new matter has been introduced. Entry of this amendment is respectfully requested.

Respectfully submitted,
HASSAN JOMAA - 4 (PCT)

Allison C. Collard, Reg.No. 22,532
Edward R. Freedman, Reg.No. 26,048
Attorneys for Applicants

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Enclosure: Abstract
Exhibit A

Express Mail No. EL 769 393 133 US
Date of Deposit June 22, 2001

I hereby certify that this paper or fee is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 C.F.R. § 1.10, on the date indicated above, and is addressed to the Ass't. Commissioner for Patents, Washington, D.C. 20231

Lisa L. Vulpis

ABSTRACT OF THE DISCLOSURE

The invention relates to the use of bisphosphonic acids of general formula (I) and derivatives thereof for the therapeutic and prophylactic treatment of infectious processes caused by viruses, bacteria, fungi or parasites in humans and animals, by deactivating the γδ T cells.

EXHIBIT A

Marked-up Version of Prior Pending
Paragraphs Showing the Changes Made

Page 1, after formula (I), replace lines 7-26 with the following paragraphs:

--in which
A_1, A_2, A_3, A_4, which may be identical or different, are selected from the group which consists of hydrogen, [substituted and unsubstituted alkyl, substituted and unsubstituted aryl, substituted and unsubstituted aralkyl, substituted and unsubstituted cycloalkyl, substituted and unsubstituted heterocyclic residue,] metals of main groups I, II and III of the periodic system, such as Na, K, Ca, Mg, Al as well as substituted and unsubstituted ammonium and ammonium compounds derived from ethylenediamine or amino acids,
X[, which may also be] is absent[,] or is selected from the group which consists of alkylene with up to 9 carbon atoms, alkenylene with up to 9 carbon atoms, [and] hydroxyalkylene with up to 9 carbon atoms and amidino,
R_1 is selected from the group which consists of H, OH, NH_2, $-CH_3$, [and] R_2[, which are identical or different, are] is selected from the group which consists of H, OH, $-NH_2$, substituted and unsubstituted acyl, substituted and unsubstituted alkyl, substituted and unsubstituted aryl, substituted and unsubstituted cycloalkyl, substituted and unsubstituted aralkyl, substituted and unsubstituted heterocyclic residue and [$-SR_3$, Cl and $-NR_3R_4$, in which R_3, R_4, which may be identical or different, are selected from the group which consists of H, OH, substituted and unsubstituted acyl, substituted and unsubstituted alkyl, substituted and unsubstituted aryl, substituted and unsubstituted aralkyl, substituted and unsubstituted aryl, substituted and unsubstituted aralkyl, substituted and unsubstituted cycloalkyl and substituted and unsubstituted heterocyclic residue, and] the pharmaceutically compatible salts, amides, esters and salts of the esters or

compounds which, on administration, form the compounds to be administered as metabolites or breakdown products,--

Page 3, replace lines 8-14 with the following paragraphs:

--Preferably suitable substances of the formula (I) are those in which

A_1, A_2, A_3, A_4, which may be identical or different, are selected from the group which consists of hydrogen, [substituted and unsubstituted alkyl, substituted and unsubstituted aryl, substituted and unsubstituted aralkyl, substituted and unsubstituted cyloalkyl, substituted and unsubstituted heterocyclic residue,] metals of main groups I, II and III of the periodic system, such as Na, K, Ca, Mg, Al, substituted and unsubstituted ammonium and ammonium compounds derived from ethylenediamine or amino acids,

X[, which may also be] is absent[,] or is selected from the group which consists of alkyl, [$(CH_2)_{0-6}$] $(CH_2)_{1-6}$, in particular $(CH_2)_{1-5}$, and amidino,--

Use of bisphosphonates for the prophylaxis and treatment of infectious processes

This invention relates to the inactivation of γδ-T cells, inter alia by the use of bisphosphonates for the therapeutic and prophylactic treatment of infections in humans and animals which are caused by viruses, bacteria, fungi and parasites.

The use of bisphosphonic acids and some of the derivatives thereof in pharmaceutical preparations is already known. The microbiostatic activity of bisphosphonic acids (DE 3 611 522), their activity in the treatment of disorders of calcium and phosphate metabolism (DE 2 534 390, DE 2 534 391, DE 3 334 211, DE 3 434 667, DE 2 745 083), their cytostatic activity (DE 3 425 812), their lipid-reducing activity (Arzneimittelforschung 46, 759-62) and their ability to stimulate immune cells (WO 97/38 696) are already known.

In order to widen the range of options for treating humans and animals, there is an urgent requirement to provide agents which are highly active.

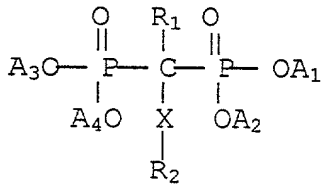
The object of the present invention is accordingly to provide a substance which is universally usable in infections by viruses, bacteria, fungi and parasites in humans and animals and which meets the above-stated requirements.

This object is utterly surprisingly achieved by the group of substances defined in claim 2. This group of substances exhibits antiinfective action against viruses, bacteria, fungi, uni- and multicellular parasites.

The immune system protects humans and animals from tumours, infections etc.. When the body is confronted with an immunogen (for example constituents of a microorganism), this brings about the multiplication and maturation of cells which are capable of combating this immunogen. Only one part of the immune system effects the actual specific immune response, with a second regulatory part providing assistance. Immunosuppression is a function of the regulatory components. These cells prevent the immune reaction from exceeding certain limits. Certain T cell populations, such as the γδ-T cells, are able to effect this immunosuppression (McMenamin et al., Science 1994 Sep. 23; 265(5180): 1869-71). These cells are stimulated by various microorganisms (Jomaa et al. FEMS Immunol. Med. Microbiol. 1999 Sep.; 25(4); 371-8). This group of pathogens includes Plasmodium falciparum, the causative organism of malaria, Mycobacterium tuberculosis, the causative organism of tuberculosis, and the Epstein-Barr virus, the causative organism of

mononucleosis. These pathogens hold the immune system in check by simulating immunosuppressive γδ-T cells, which means that no proper immune defence comes into effect. As a result, the microorganisms are able to exist in the host and persist for a very long time.

It has now been found that substances of the general formula (I)



(I),

in which

A_1, A_2, A_3, A_4, which may be identical or different, are selected from the group which consists of hydrogen, substituted and unsubstituted alkyl, substituted and unsubstituted aryl, substituted and unsubstituted aralkyl, substituted and unsubstituted cycloalkyl, substituted and unsubstituted heterocyclic residue, metals of main groups I, II and III of the periodic system, such as Na, K, Ca, Mg, Al as well as substituted and unsubstituted ammonium and ammonium compounds derived from ethylenediamine or amino acids,

X, which may also be absent, is selected from the group which consists of alkylene, alkenylene and hydroxyalkylene,

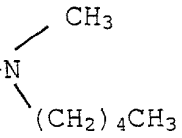
R_1 and R_2, which are identical or different, are selected from the group which consists of H, OH, $-NH_2$, substituted and unsubstituted acyl, substituted and unsubstituted alkyl, substituted and unsubstituted aryl, substituted and unsubstituted cycloalkyl, substituted and unsubstituted aralkyl, substituted and unsubstituted heterocyclic residue and $-SR_3$, Cl and $-NR_3R_4$, in which R_3, R_4, which may be identical or different, are selected from the group which consists of H, OH, substituted and unsubstituted acyl, substituted and unsubstituted alkyl, substituted and unsubstituted aryl, substituted and unsubstituted aralkyl, substituted and unsubstituted cycloalkyl and substituted and unsubstituted heterocyclic residue, and

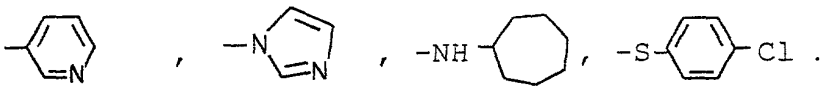
the pharmaceutically compatible salts, amides, esters and salts of the esters or compounds which, on administration, form the compounds to be administered as metabolites or breakdown products,

result in inactivation of the γδ-T cells in humans and animals. These substances are accordingly suitable for the treatment and prophylaxis of infectious diseases caused by parasites, bacteria and viruses. In particular, these substances are suitable for the eradication

of persistent infectious organisms including Helicobacter pylori, Chlamydia and hepatitis C virus.

These substances are furthermore suitable as an adjuvant to vaccines to strengthen the immune response to vaccinations.

Preferably suitable substances of the formula (I) are those in which
A_1, A_2, A_3, A_4, which may be identical or different, are selected from the group which consists of hydrogen, substituted and unsubstituted alkyl, substituted and unsubstituted aryl, substituted and unsubstituted aralkyl, substituted and unsubstituted cycloalkyl, substituted and unsubstituted heterocyclic residue, metals of main groups I, II and III of the periodic system, such as Na, K, substituted and unsubstituted ammonium and ammonium compounds derived from ethylenediamine or amino acids,
X, which may also be absent, is selected from the group which consists of alkyl, $(CH_2)_{0-6}$, in particular $(CH_2)_{1-5}$, and amidino,
R_1 is selected from the group which consists of H, OH, NH_2, $-CH_3$, and
R_2 is selected from the group which consists of $-NH_2$, 



Special features of the above definitions and suitable examples thereof are given below:

"Acyl" is a substituent which originates from an acid, such as from an organic carboxylic acid, carbonic acid, carbamic acid or the thio acid or imidic acid corresponding to the above individual acids, or from an organic sulfonic acid, wherein these acids in each case comprise aliphatic, aromatic and/or heterocyclic groups in the molecule together with carbamoyl or carbamimidoyl.

Suitable examples of these acyl groups are given below.
Aliphatic acyl groups are defined as acyl residues originating from an aliphatic acid and include the following:
alkanoyl (for example formyl, acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl,

pivaloyl etc.); alkenoyl (for example acryloyl, methacryloyl, crotonoyl etc.); alkylthioalkanoyl (for example methylthioacetyl, ethylthioacetyl etc.); alkanesulfonyl (for example mesyl, ethanesulfonyl, propanesulfonyl etc.); alkoxycarbonyl (for example methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl etc.); alkylcarbamoyl (for example methylcarbamoyl etc.); (N-alkyl)thiocarbamoyl (for example (N-methyl)thiocarbamoyl etc.); alkylcarbamimidoyl (for example methylcarbamimidoyl etc.); oxalo; alkoxalyl (for example methoxalyl, ethoxalyl, propoxalyl etc.).

In the above examples of aliphatic acyl groups, the aliphatic hydrocarbon moiety, in particular the alkyl group or alkane residue, may optionally have one or more suitable substituents, such as amino, halogen (for example fluorine, chlorine, bromine etc.), hydroxy, hydroxyimino, carboxy, alkoxy (for example methoxy, ethoxy, propoxy etc.), alkoxycarbonyl, acylamino (for example benzyloxycarbonylamino etc.), acyloxy (for example acetoxy, benzoyloxy etc.) and the like; preferred aliphatic acyl residues with such substituents which may be mentioned are, for example, alkanoyls substituted with amino, carboxy, amino and carboxy, halogen, acylamino or the like.

Aromatic acyl residues are defined as those acyl residues which originate from an acid with a substituted or unsubstituted aryl group, wherein the aryl group may comprise phenyl, tolyl, xylyl, naphthyl and the like; suitable examples are stated below:
aroyl (for example benzoyl, toluoyl, xyloyl, naphthoyl, phthaloyl etc.); aralkanoyl (for example phenylacetyl etc.); aralkenoyl (for example cinnamoyl etc.); aryloxyalkanoyl (for example phenoxyacetyl etc.); arylthioalkanoyl (for example phenylthioacetyl etc.); arylaminoalkanoyl (for example N-phenylglycyl, etc.); arenesulfonyl (for example benzenesulfonyl, tosyl or toluenesulfonyl, naphthalenesulfonyl etc.); aryloxycarbonyl (for example phenoxycarbonyl, naphthyloxycarbonyl etc.); aralkoxycarbonyl (for example benzyloxycarbonyl etc.); arylcarbamoyl (for example phenylcarbamoyl, naphthylcarbamoyl etc.); arylglyoxyloyl (for example phenylglyoxyloyl etc.).

In the above-stated Examples of aromatic acyl residues, the aromatic hydrocarbon moiety (in particular the aryl residue) and/or the aliphatic hydrocarbon moiety (in particular the alkane residue) may optionally have one or more suitable substituents, such as those which have already been stated as suitable substituents for the alkyl group or the alkane residue. Examples of preferred aromatic acyl residues with specific substituents which may in particular be mentioned are aroyl substituted with halogen and hydroxy or with halogen and

acyloxy, and aralkanoyl substituted with hydroxy, hydroxyimino, dihaloalkanoyloxyimino, together with arylthiocarbamoyl (for example phenylthiocarbamoyl etc.); arylcarbamimidoyl (for example phenylcarbamimidoyl etc.).

A heterocyclic acyl residue is taken to mean an acyl residue which originates from an acid with a heterocyclic group; such residues include:

heterocyclic carbonyl, in which the heterocyclic residue is an aromatic or aliphatic 5- to 6-membered heterocycle with at least one heteroatom from the group nitrogen, oxygen and sulfur (for example thiophenyl, furoyl, pyrrolecarbonyl, nicotinyl etc.);

heterocycle-alkanoyl, in which the heterocyclic residue is 5- to 6-membered and comprises at least one heteroatom from the group nitrogen, oxygen and sulfur (for example thiophenylacetyl, furylacetyl, imidazolylpropionyl, tetrazolylacetyl, 2-(2-amino-4-thiazolyl)-2-methoxyiminoacetyl etc.) and the like.

In the above Examples of heterocyclic acyl residues, the heterocycle and/or the aliphatic hydrocarbon moiety may optionally comprise one or more suitable substituents, such as the same as were stated to be suitable for alkyl and alkane groups.

"Alkyl" is a linear or branched alkyl residue with up to 9 carbon atoms, such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert.-butyl, pentyl, hexyl and the like.

Cycloalkyl preferably denotes an optionally substituted C_3-C_7 cycloalkyl; possible substituents are inter alia alkyl, alkenyl, alkynyl, alkoxy (for example methoxy, ethoxy etc.), halogen (for example fluorine, chlorine, bromine etc.), nitro and the like.

Aryl is an aromatic hydrocarbon residue, such as phenyl, naphthyl etc., which may optionally comprise one or more suitable substituents, such as alkyl, alkenyl, alkynyl, alkoxy (for example methoxy, ethoxy etc.), halogen (for example fluorine, chlorine, bromine etc.), nitro and the like.

"Aralkyl" includes mono-, di-, triphenylalkyls such as benzoyl, phenethyl, benzhydryl, trityl and the like, wherein the aromatic moiety may optionally comprise one or more suitable substituents, such as alkoxy (for example methoxy, ethoxy etc.), halogen (for example fluorine, chlorine, bromine etc.), nitro and the like.

"Alkylene" includes linear or branched alkylene groups, which comprise up to 9 carbon atoms and may be represented by the formula

$-(C_nH_{2n})-$

in which n is an integer from 1 to 9, such as methylene, ethylene, trimethylene, methylethylene, tetramethylene, 1-methyltrimethylene, 2-ethylethylene, pentamethylene, 2-methyltetramethylene, isopropylethylene, hexamethylene and the like; preferred alkylene residues have up to 4 carbon atoms and particularly preferred residues are those with 3 carbon atoms, such as for example trimethylene.

"Alkenylene" includes linear or branched alkenylene groups having up to 9 carbon groups which may be represented by the formula

$-(C_nH_{2n-2})-$

in which n is an integer from 2 to 9, such as for example vinylene, propenylene (for example 1-propenylene, 2-propenylene), 1-methylpropenylene, 2-methylpropenylene, butenylene, 2-ethylpropenylene, pentenylene, hexenylene and the like; the alkenylene residue may particularly preferably have up to 5 carbon atoms and in particular 3 carbon atoms, such as for example 1-propenylene.

"Hydroxyalkylene" includes linear or branched alkylene residues, which have up to 9 carbon atoms, wherein one or more selected carbon atoms is/are substituted with a hydroxy group; these residues may be reproduced by the formula

$-(C_nH_{2n-z})(OH)_z-$

in which n is an integer from 1 to 9 and z is an integer from 1 to 9, where $z \leq n$ applies. Suitable examples of hydroxyalkylene groups are hydroxymethylene, hydroxyethylene (for example 1-hydroxyethylene and 2-hydroxyethylene), hydroxytrimethylene (for example 1-hydroxytrimethylene, 2-hydroxytrimethylene and 3-hydroxytrimethylene), hydroxytetramethylene (for example 2-hydroxytetramethylene), 2-hydroxy-2-methyltrimethylene, hydroxypentamethylene (for example 2-hydroxypentamethylene), hydroxyhexamethylene (for example 2-hydroxyhexamethylene) and the like. A particularly preferred hydroxyalkylene is one comprising up to 4 carbon atoms and in particular such a compound comprising 3 carbon atoms, such as for example hydroxytrimethylene.

"Heterocyclic residue" is preferably an aromatic or aliphatic 5- to 6-membered heterocycle with at least one heteroatom from the group nitrogen, oxygen and sulfur (for example thiophenyl, furoyl, pyrrolecarbonyl, nicotinoyl etc.).

The following have proved to be particularly active bisphosphonic acids
amino-hydroxy-methylidene-bisphosphonic acid (AMP),
2-amino-1-hydroxyethylidene-1,1-bisphosphonic acid (AEP),
3-amino-1-hydroxypropylidene-1,1-bisphosphonic acid (pamidronic acid),
4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid (alendronic acid),
6-amino-1-hydroxyhexylidene-1,1-bisphosphonic acid (AHP),
amidinomethylene-bisphosphonic acid (AIMP),
3-methylpentylamino-1-hydroxypropylidene-1,1-bisphosphonic acid (ibandronic acid),
2-(3-pyridinyl)-1-hydroxyethylidene-bisphosphonic acid (risedronic acid),
1-hydroxy-2-(imidazol-1-yl)-ethylidene-1,1-bisphosphonic acid (zoledronic acid),
cycloheptylaminomethylenediphosphonic acid (cimadronic acid),
4-chlorophenyl-thiomethylene-1,1-bisphosphonic acid (tiludronic acid) and the derivatives thereof.

The compounds are in particular suitable for the therapeutic and prophylactic treatment of infections in humans and animals caused by viruses, bacteria, uni- and multicellular parasites and fungi.

The bisphosphonic acids and the derivatives thereof are suitable for the treatment of acne vulgaris, tuberculosis in humans and animals, leprosy and further mycobacterioses in humans and animals, paratuberculosis in animals, Campylobacter enteritis infections in humans and animals.

Use is furthermore in particular preferred in the eradication of Helicobacter in ulcers of the gastrointestinal tract.

The substances are furthermore in particular suitable for the eradication of Chlamydia for the prevention or treatment of cardiac and vascular diseases, in particular coronary cardiac disease.

Combination treatment with another antibiotic may also be used to treat the above-stated diseases. Isoniazid, rifampicin, ethambutol, pyrazinamide, streptomycin, protionamide and dapsone are in particular suitable for combination preparations with other antiinfective agents for the treatment of tuberculosis.

The bisphosphonates according to the invention are suitable for combating the following viral infections:
eradication of papillomaviruses to prevent tumours, in particular tumours of the reproductive organs caused by papillomaviruses in humans, eradication of herpesviruses, eradication of human herpesvirus 8 to treat Kaposi's sarcoma, eradication of cytomegaloviruses before transplantations, eradication of Epstein-Barr viruses before transplantation and to prevent tumours associated with Epstein-Barr viruses, eradication of hepatitis viruses to treat chronic liver disease and to prevent liver tumours and cirrhosis of the liver, eradication of coxsackie-viruses in cardiomyopathy, eradication of coxsackie-viruses in diabetes mellitus patients, eradication of immunodeficiency viruses in humans and animals, treatment of accompanying infections in AIDS patients, treatment of respiratory tract inflammation of viral causation (laryngeal papilloma, hyperplasia, rhinitis, pharyngitis, bronchitis, pneumonia), of the liver and gall system (hepatitis, cholangitis, hepatocellular carcinoma), of the lymphatic tissue (mononucleosis, lymphadenitis), of the haemopoietic system, of the skin (warts, dermatitis, herpes labialis, herpes febrilis, herpes zoster, shingles), of the mucous membranes (papillomas, conjunctival papillomas, hyperplasia, dysplasia), of the cardiovascular system (arteriitis, myocarditis, endocarditis, pericarditis), of the kidney/urinary system, of the reproductive organs (anogenital lesions, warts, genital warts, sharp condylomas, dysplasia, papillomas, cervical dysplasia, condyloma acuminatum, epidermodysplasia verruciformis), of the locomotory organs (myositis, myalgia).

The agents may be used in combination with other agents having antiviral properties.

Preferred pharmaceutical preparations which may be mentioned are tablets, coated tablets, capsules, pills, granules, suppositories, solutions, suspensions and emulsions, pastes, ointments, gels, creams, lotions, powders and sprays. Tablets, coated tablets, capsules, pills and granules may contain the active substances together with conventional excipients, such as (a) fillers and extenders, for example starches, lactose, cane sugar, glucose, mannitol and silica, (b) binders, for example carboxymethylcellulose, alginates, gelatine, polyvinylpyrrolidone, (c) humectants, for example glycerol, (d) suspending agents, for example agar-agar, calcium carbonate and sodium carbonate, (e) dissolution retardants, for example paraffin and (f) resorption accelerators, for example quaternary ammonium compounds, (g) wetting agents, for example cetyl alcohol, glycerol monostearate, (h) adsorbents, for example kaolin and bentonite and (i) lubricants, for example talcum, calcium and magnesium stearate and solid polyethylene glycols or mixtures of the substances stated in (a) to (i).

The tablets, coated tablets, capsules, pills and granules may be provided with conventional coatings and shells optionally containing opacifying agents and may also be composed such that they release the active substances only with a delay or preferably in a particular part of the intestinal tract, wherein polymeric substances and waxes may, for example, be used as the matrices.

The active substance or substances, optionally together with one or more of the above-stated excipients, may also be present in microencapsulated form.

In addition to the active substance or substances, suppositories may contain conventional water-soluble or water-insoluble excipients, for example polyethylene glycols, fats, for example cocoa butter and higher esters (for example C_{14} alcohol with C_{16} fatty acid) or mixtures of these substances.

In addition to the active substance or substances, ointments, pastes, creams and gels may contain conventional excipients, for example animal and vegetable fats, waxes, paraffins, starch, gum tragacanth, cellulose derivatives, polyethylene glycols, silicones, bentonites, silica, talcum and zinc oxide or mixtures of these substances.

In addition to the active substance or substances, powders and sprays may contain conventional excipients, for example lactose, talcum, silica, aluminium hydroxide, calcium silicate and polyamide powder or mixtures of these substances. Sprays may additionally contain conventional propellants, for example chlorofluorocarbons.

In addition to the active substance or substances, solutions and emulsions may contain conventional excipients, such as solvents, solubilising agents and emulsifiers, for example water, ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils, in particular cottonseed oil, peanut oil, corn oil, olive oil, castor oil and sesame oil, glycerol, glycerol formal, tetrahydrofurfuryl alcohol, polyethylene glycols and sorbitan fatty acid esters or mixtures of these substances.

For parenteral administration, the solutions and emulsions may also be present in sterile, isotonic form.

In addition to the active substance or substances, suspensions may contain conventional excipients, such as liquid diluents, for example water, ethyl alcohol, propylene glycol, suspending agents, for example ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminium metahydroxide, bentonite, agar-agar and gum tragacanth or mixtures of these substances.

The stated formulations may also contain colorants, preservatives and odour- or flavour-enhanced additives, for example peppermint oil and eucalyptus oil, and sweeteners, for example saccharin.

Bisphosphonic acids and the derivatives thereof of the formula (I) should preferably be present in the pharmaceutical preparations listed above in a concentration of approx. 0.1 to 99.5 wt.%, preferably from approx. 0.5 to 95 wt.%, of the complete mixture.

Apart from the compounds of the formula (I), the pharmaceutical preparations listed above may also contain further pharmaceutical active substances.

The above-stated pharmaceutical preparations are produced in the conventional manner using known methods, for example by mixing the active substance or substances with the excipient or excipients.

The stated preparations may be administered to humans and animals orally, rectally, parenterally (intravenously, intramuscularly, subcutaneously), intracisternally, intravaginally, intraperitoneally, topically (powders, ointments, drops) and for the treatment of infections in cavities, body cavities. Suitable preparations which may be considered are solutions for injections, solutions and suspensions for oral therapy, gels, infusion formulations, emulsions, ointments or drops. Topical treatment may be performed using ophthalmological and dermatological formulations, silver and other salts, ear drops, eye ointments, powders or solutions. Administration to animals may also be achieved via the feed or drinking water in suitable formulations. Gels, pulverulent formulations, powders, tablets, controlled-release tablets, premixes, concentrates, granules, pellets, tablets, boli, capsules, aerosols, sprays, inhalation formulations may also be used in humans and animals. The compounds according to the invention may also be incorporated into other supports, such as for example plastics (plastic chains for topical treatment), collagen or bone cement.

There is a very wide range of variation in the quantity of the individual derivatives necessary to achieve the desired effect. It has in general proved advantageous in both human and veterinary medicine to administer the bisphosphonates of the formula (I) in total quantities of approx. 0.005 to approx. 200 mg/kg body weight per 24 hours, optionally in the form of two or more individual doses in order to achieve the desired results. An individual dose preferably contains the active substance or substances in quantities of approx. 0.002 to approx. 50 mg/kg body weight. It may, however, be necessary to deviate from the stated dosages, in particular as a function of the nature and body weight of the patient to be treated, the nature and severity of the disease, the nature of the preparations and the route of administration of the pharmaceutical preparation and the period of time over which administration is performed.

In some cases, it may accordingly be sufficient to use less than the above-stated quantity of active substance, while in other cases more than the above-stated quantity of active substance must be used. The person skilled in the art will use his/her skill to determine the optimum dosage and route of administration required in each particular case.

Animals may be treated with the compounds used according to the invention by administration in conventional concentrations and preparations together with feed or feed preparations or with drinking water.

Some examples of activity are listed below:

Example 1

Healthy test subjects received an infusion of 90 mg of pamidronic acid at fortnightly intervals. After the third infusion, a blood sample was taken from the subjects. The mononuclear cells were isolated from the blood. The activatability of the γδ-T cells was then tested. A full description is published in Jomaa et al. FEMS Immunol. Med. Microbiol. 1999 Sep.; 25(4); 371-8.

The cells from the treated subjects exhibit no γδ-T cell activation by antigens obtained from microorganisms. In contrast, cells from control subjects could be activated.

Example 2

The cells of test subjects who had been treated with ibandronic acid (1 mg per treatment) in accordance with the protocol from Example 1 exhibited no γδ-T cell activation by antigens which had been obtained from microorganisms.

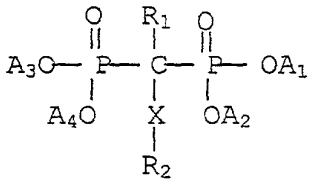
Example 3

The cells of test subjects who had been treated with zoledronic acid in accordance with the protocol from Examples 1 and 2 exhibited no γδ-T cell activation by antigens which had been obtained from microorganisms.

Patent Claims

1. Inactivation of the γδ-T cells for the prevention and treatment of diseases caused by parasites, viruses, bacteria and fungi.

2. Use of bisphosphonic acids of the general formula



(I),

in which

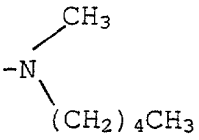
A_1, A_2, A_3, A_4, which may be identical or different, are selected from the group which consists of hydrogen, substituted and unsubstituted alkyl, substituted and unsubstituted aryl, substituted and unsubstituted aralkyl, substituted and unsubstituted cycloalkyl, substituted and unsubstituted heterocyclic residue, metals of main groups I, II and III of the periodic system, such as Na, K, Ca, Mg, Al as well as substituted and unsubstituted ammonium and ammonium compounds derived from ethylenediamine or amino acids,

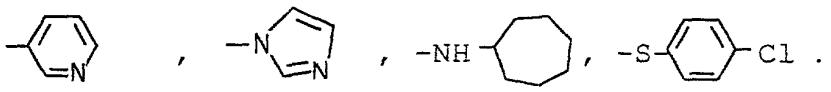
X, which may also be absent, is selected from the group which consists of alkylene, alkenylene and hydroxyalkylene,

R_1 and R_2, which are identical or different, are selected from the group which consists of H, OH, $-NH_2$, substituted and unsubstituted acyl, substituted and unsubstituted alkyl, substituted and unsubstituted aryl, substituted and unsubstituted cycloalkyl, substituted and unsubstituted aralkyl, substituted and unsubstituted heterocyclic residue and $-SR_3$, Cl and $-NR_3R_4$, in which

R_3, R_4, which may be identical or different, are selected from the group which consists of H, OH, substituted and unsubstituted acyl, substituted and unsubstituted alkyl, substituted and unsubstituted aryl, substituted and unsubstituted aralkyl, substituted and unsubstituted cycloalkyl and substituted and unsubstituted heterocyclic residue, and the pharmaceutically compatible salts, amides, esters and salts of the esters or compounds which, on administration, form the compounds to be administered as metabolites or breakdown products, for inactivating γδ-T cells.

3. Use according to claim 2, characterised in that

A_1, A_2, A_3, A_4, which may be identical or different, are selected from the group which consists of hydrogen, substituted and unsubstituted alkyl, substituted and unsubstituted aryl, substituted and unsubstituted aralkyl, substituted and unsubstituted cycloalkyl, substituted and unsubstituted heterocyclic residue, metals of main groups I, II and III of the periodic system, such as Na, K, substituted and unsubstituted ammonium and ammonium compounds derived from ethylenediamine or amino acids,
X, which may also be absent, is selected from the group which consists of alkyl, $(CH_2)_{0-6}$, in particular $(CH_2)_{1-5}$, and amidino,
R_1 is selected from the group which consists of H, OH, NH_2, $-CH_3$, and
R_2 is selected from the group which consists of $-NH_2$, 



4. Use according to claim 3,
characterised in that
the bisphosphonates are selected from the group which consists of amino-hydroxy-methylidene-bisphosphonic acid,
2-amino-1-hydroxyethylidene-1,1-bisphosphonic acid
3-amino-1-hydroxypropylidene-1,1-bisphosphonic acid,
4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid,
6-amino-1-hydroxyhexylidene-1,1-bisphosphonic acid,
amidinomethylene-bisphosphonic acid,
3-methylpentylamino-1-hydroxypropylidene-1,1-bisphosphonic acid,
2-(3-pyridinyl)-1-hydroxyethylidene-bisphosphonic acid,
1-hydroxy-2-(imidazol-1-yl)-ethylidene-1,1-bisphosphonic acid,
cycloheptylaminomethylenediphosphonic acid,
4-chlorophenyl-thiomethylene-1,1-bisphosphonic acid and the derivatives thereof.

5. Use according to one of the preceding claims for the treatment and prophylaxis of acne vulgaris, tuberculosis in humans and animals, leprosy and further mycobacterioses in humans and animals, paratuberculosis in animals, Campylobacter enteritis infections in

humans and animals, of Helicobacter pylori and Chlamydia for the prevention or treatment of cardiac and vascular diseases, in particular coronary cardiac disease.

6. Use according to one of claims 1 to 4 in the eradication of bacteria and viruses.

7. Use according to claim 6 for the eradication of Helicobacter pylori and Chlamydia.

8. Use according to claim 6 for the eradication of eradication of papillomaviruses to prevent tumours, in particular tumours of the reproductive organs caused by papillomaviruses in humans, eradication of herpesviruses, eradication of human herpesvirus 8 to treat Kaposi's sarcoma, eradication of cytomegaloviruses before transplantations, eradication of Epstein-Barr viruses before transplantation and to prevent tumours associated with Epstein-Barr viruses, eradication of hepatitis viruses to treat chronic liver disease and to prevent liver tumours and cirrhosis of the liver, eradication of coxsackie-viruses in cardiomyopathy, eradication of coxsackie-viruses in diabetes mellitus patients, eradication of immunodeficiency viruses in humans and animals, treatment of accompanying infections in AIDS patients, treatment of respiratory tract inflammation of viral causation (laryngeal papilloma, hyperplasia, rhinitis, pharyngitis, bronchitis, pneumonia), of the liver and gall system (hepatitis, cholangitis, hepatocellular carcinoma), of the lymphatic tissue (mononucleosis, lymphadenitis), of the haemopoietic system, of the skin (warts, dermatitis, herpes labialis, herpes febrilis, herpes zoster, shingles), of the mucous membranes (papillomas, conjunctival papillomas, hyperplasia, dysplasia), of the cardiovascular system (arteriitis, myocarditis, endocarditis, pericarditis), of the kidney/urinary system, of the reproductive organs (anogenital lesions, warts, genital warts, sharp condylomas, dysplasia, papillomas, cervical dysplasia, condyloma acuminatum, epidermodysplasia verruciformis), of the locomotory organs (myositis, myalgia).

9. Use according to claim 8 for the eradication of the hepatitis C virus.

10. Use according to one of the preceding claims in a pharmaceutical preparation which additionally contains a pharmaceutically acceptable excipient.

11. Use according to one of the preceding claims as an adjuvant to vaccines.

COMBINED DECLARATION FOR PATENT APPLICATION AND POWER OF ATTORNEY (Includes Reference to PCT International Applications)	ATTORNEY'S DOCKET NUMBER JOMAA-4 PCT

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name,

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

USE OF BISPHOSPHONATES FOR THE PROPHYLAXIS AND TREATMENT OF INFECTIOUS PROCESSES

the specification of which (check only one item below):

[ ] is attached hereto.

[ ] was filed as United States application

Serial No. _____

on _____,

and was amended

on _____ (if applicable).

[X] was filed as PCT international application

Number PCT/EP99/10350

on 23 DECEMBER 1999,

and was amended under PCT Article 19

on _____ (if applicable).

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations, §1.56(a).

I hereby claim foreign priority benefits under Title 35, United States Code, §119 of any foreign application(s) for patent or inventor's certificate or of any PCT international application(s) designating at least one country other than the United States of America listed below and have also identified below any foreign application(s) for patent or inventor's certificate or any PCT international application(s) designating at least one country other than the United States of America filed by me on the same subject matter having a filing date before that of the application(s) of which priority is claimed:

PRIOR FOREIGN/PCT APPLICATION(S) AND ANY PRIORITY CLAIMS UNDER 35 U.S.C. 119:

COUNTRY (if PCT, indicate "PCT")	APPLICATION NUMBER	DATE OF FILING (day, month, year)	PRIORITY CLAIMED UNDER 35 USC 119
GERMANY	198 59 668.5	23 DECEMBER 1998	[X] YES [ ] NO
			[ ] YES [ ] NO
			[ ] YES [ ] NO
			[ ] YES [ ] NO
			[ ] YES [ ] NO

COMBINED DECLARATION FOR PATENT APPLICATION AND POWER OF ATTORNEY (Includes Reference to PCT International Applications)	ATTORNEY'S DOCKET NUMBER JOMAA-4 PCT

I hereby claim the benefit under Title 35, United States Code, Section 119(e) of any United States provisional application(s) listed below.

(Application Number) (Filing Date)

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) or PCT international application(s) designating the United States of America that is/are listed below and, insofar as the subject matter of each of the claims of this application is not disclose in that/those prior application(s) in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, §1.56(a) which occurred between the filing date of the prior application(s) and the national or PCT international filing date of this application:

PRIOR U.S. APPLICATIONS OR PCT INTERNATIONAL APPLICATIONS DESIGNATING THE U.S. FOR BENEFIT UNDER 35 U.S.C. 120:

U.S. APPLICATIONS		STATUS (Check One)		
U.S. APPLICATION NUMBER	U.S. FILING DATE	PATENTED	PENDING	ABANDONED

PCT APPLICATIONS DESIGNATING THE U.S.					
PCT APPLICATION NO.	PCT FILING DATE	U.S. SERIAL NUMBERS ASSIGNED (if any)			

POWER OF ATTORNEY: As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith. (List name and registration numbers): KURT KELMAN, Registration No. 18,628
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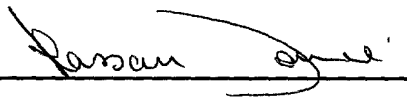
1	POST OFFICE ADDRESS	POST OFFICE ADDRESS: FRANKFURTER STRASSE 50	CITY: D-35392 GIESSEN	STATE & ZIP CODE/COUNTRY: GERMANY

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

SIGNATURE OF INVENTOR 201

X 

DATE 06.06.2001

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